Symptom onset and treatment in acute myocardial infarction

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CHAPTER 8

Usefulness of thrombus aspiration for the treatment of coronary stent thrombosis

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ABSTRACT

Background: Current treatment for coronary stent thrombosis (ST) often lacks satisfactory results and clinical outcome is poor. We investigated the impact of manual thrombus aspiration during percutaneous coronary intervention (PCI) on myocardial reperfusion and clinical outcome in patients with angiographically proven ST.

Methods: We interrogated our PCI registry for patients with a first stent placement between January 2002 and May 2010 who had undergone an emergent repeated PCI procedure and systematically reviewed the coronary angiograms and hospital records for evidence of ST.

Results: We identified 113 patients with ST. Thrombus aspiration was used in 51 patients and 62 patients received conventional PCI. Histopathological analysis of thrombus aspirates was performed in 6 patients. The use of thrombus aspiration predicted postprocedural TIMI 3 flow (odds ratio 3.16; 95% confidence interval 1.22-8.17; P=0.018) and myocardial blush grade 2/3 (odds ratio 3.20; 95% confidence interval 1.20-8.55; P=0.020), after multivariable adjustment with bootstrap model selection. Distal embolization was lower in the thrombus aspiration group compared with the conventional PCI group (14% vs. 37%; P=0.017). In most patients, aspirated thrombus was large and contained platelet and erythrocyte components at histopathological analysis. Mortality in the thrombus aspiration group and conventional PCI group was 9.8% vs. 16% at 30 days (P=0.351) and 12% vs. 21% at 1 year (P=0.220), respectively.

Conclusions: The use of manual thrombus aspiration in patients with ST was associated with greater epicardial and microvascular myocardial reperfusion. In addition, mortality was lower in patients treated with thrombus aspiration, although not statistically significant.

INTRODUCTION

Thrombus aspiration during primary percutaneous coronary intervention (PCI) has shown to improve myocardial reperfusion and may decrease mortality in patients with ST-elevation myocardial infarction (STEMI).[1-3] Although emerging in STEMI, the role of thrombus aspiration in patients with coronary stent thrombosis (ST) has not been studied extensively. In the current study, we sought to investigate the impact of manual thrombus aspiration during PCI on myocardial reperfusion and clinical outcome in patients with angiographic evidence of ST (i.e. definite ST).

METHODS

Study design

Data on all patients undergoing PCI is routinely collected in our center. In order to identify patients with ST, we performed a systematic search in our electronic database on all repeated PCI procedures performed in 11346 patients who had undergone a first stent placement between January 2002 and May 2010 at our center. After filtering out elective repeated PCI procedures, all remaining coronary angiograms were systematically reviewed for evidence of ST by an experienced cardiologist (FZ). Subsequently, ST was independently confirmed by two experienced cardiologists (BJS or AFH) based on coronary angiograms and hospital records. Also, subsequent angiograms and hospital records were reviewed for occurrence of target vessel revascularization (TVR) and recurrence of ST (re-ST). Baseline characteristics and follow-up were collected from a prospectively recorded database and missing data was completed by hospital record review as well as telephone interviews. Follow-up with regard to all-cause 30-day and 1-year mortality was collected using municipal civil registries. These registries provide completeness of follow-up regarding vital status in >99% of patients admitted to our department. All patients with definite ST were included in this analysis.

Treatment

All patients underwent PCI and were pretreated with aspirin (500 mg), clopidogrel (600 mg), and heparin (5000 IU). Periprocedural glycoprotein IIb/IIIa inhibitors were used, unless contra-indicated. Thrombus aspiration was performed at the operator's discretion. For all patients, the first procedural step was the passing of a steerable guidewire through the target lesion. For patients in the "thrombus aspiration" group, this step was followed by the advancing of a 6-French Export Aspiration Catheter (Medtronic, Minneapolis, Minnesota) or a 6-French Diver Clot Extraction Catheter (Invatec, Bethlehem, Pennsylvania) into the target coronary segment during continuous aspiration. For patients in the "conventional PCI" group, this step was followed by balloon dilatation to establish antegrade flow. When judged necessary by the operator, additional balloon dilatation and/or stent placement was performed in both groups. Patients were categorized into the thrombus aspiration group when thrombus aspiration was attempted, regardless of its success. Since all patients had ST, aspirin was usually prescribed indefinitely and clopidogrel for at least 1 year.

Histopathological analysis

Thrombus aspiration was deemed successful when thrombotic material was retrieved. In 6 patients,

histopathological analysis of filtered material obtained by thrombus aspiration was performed. Material was placed in formalin and fixed for 24 hours. Thereafter, filtered material was pelleted by centrifugation in liquid agar 65°C in an Eppendorf tube. After the agar pellet was solidified at 4°C, it was embedded in paraffin using an automated tissue processor. Paraffin sections were cut at 4 µm and stained with hematoxylin-eosin for microscopical examination (x100). Immunostaining was performed to optimize visualization of endothelial cells, smooth muscle cells, and macrophage foam cells. Identified material was analyzed for the presence of 3 components: platelets, erythrocytes, and atheromatous plaque (defined as any fragment of vessel wall, cholesterol crystals, inflammatory cells, or collagen tissue). Size was classified into 5 groups: residue (very small filter casts of loosely cohesive platelets), well-formed thrombi smaller than 0.5 mm, 0.5 to 1.0 mm, 1.0 to 2.0 mm, and >2 mm.

Definitions and enpoints

ST was defined as an acute coronary syndrome with angiographic evidence of thrombus or occlusion, thereby meeting the Academic Research Consortium (ARC) criteria for 'definite' ST.[4] Furthermore, patients were classified into timing of ST by ARC classification: early ST (onset of ST 0-30 days after initial stent placement), late ST (31-360 days), and very late ST (>360 days). Hypertension and hypercholesterolemia were defined as a documented history of this condition warranting medical therapy. Ischemic time was defined as time from symptom onset to initial intracoronary therapy by means of thrombus aspiration or balloon inflation of the infarct related coronary artery. TIMI flow and myocardial blush grade were recorded as previously described.[5,6] Lesion calcium was identified as radio-opacities within the vascular wall of the target vessel on the angiogram. When multiple stents were placed, total stent length was defined as the sum of the individual stent lengths placed in the target coronary artery and minimal stent diameter was defined as the smallest diameter of any stent placed in the target coronary artery. Postprocedural distal embolization was defined as an angiographically visible distal filling defect with abrupt cut-off in the vessel located distally of the ST related lesion.[7] Distal embolization could be assessed when epicardial coronary flow was present through the infarct-related lesion and the distal vessels were visualized. TIMI thrombus grade at the target lesion site was defined according to Gibson et al.[8] Myocardial infarction was defined as recurrent symptoms with new ST-segment elevation and elevation of the levels of cardiac markers to

at least twice the upper limit of the normal range. Re-ST was defined as recurrence of definite ST in the target vessel according to the ARC criteria.[4] TVR was defined as ischemia-driven revascularization of the ST related vessel, performed by means of PCI or coronary artery bypass grafting (CABG). Occurrence of major adverse cardiac events (MACE) was defined as death, myocardial infarction, re-ST, or TVR.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median and interquartile range. Discrete variables were presented as fractions and percentages. To calculate P-values, we used Student's t-test for normally distributed continuous variables, Mann-Whitney U for nonparametric continuous variables, and Pearson's χ^2 test for categorical variables. For ordinal variables, the P-value for trend was obtained. Occurrence of MACE and its separate components was estimated and plotted using the Kaplan-Meier method and tested with the Log Rank test.

Multivariable logistic regression models with bootstrap model selection were fitted to assess independent predictors of postprocedural TIMI 3 flow and postprocedural myocardial blush grade 2 or 3. This method has been used previously in the context of a ST population to avoid an over fit model.[9] Among all baseline and procedural characteristics listed in Table 1 and 2, potential predictors of postprocedural TIMI 3 flow and myocardial blush grade 2 or 3 with a P-value <0.15 in univariable analysis were selected for multivariable analysis. For these variables, bootstrap selection with 200 models was performed. Predictors selected in more than 140 of the models (70%) were included in the final model. Goodness of fit was assessed with the Hosmer Lemeshow test. A potentially confounding effect of improvements other than thrombus aspiration throughout our study period was investigated in our multivariable models, but was found to be absent. For all analyses, a P-value <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed with SPSS, version 16.0.2 (SPSS Inc., Chicago, Illinois) and Stata, version 11.0 (StataCorp, College Station, Texas).

RESULTS

Between January 2002 and May 2010, 11346 patients underwent a first coronary stent implantation at our center. Among this group, 113 patients (1.0%) later presented with definite ST and were treated with PCI; 51 patients (45%) were treated with thrombus aspiration and 62 patients (55%) were treated with conventional PCI. PCI

Table 1. Baseline characteristics

Variable	Thrombus aspiration *(n=51)*	Conventional PCI *(n=62)*	P
Age (years)	64 ± 13	63 ± 13	0.611
Men	43 (84)	44 (71)	0.093
Body mass index (kg/m^2)	28 ± 5.2	27 ± 4.0	0.729
Systolic blood pressure (mm Hg)	112 ± 24	115 ± 28	0.612
Systolic blood pressure <90 mm Hg	7 (16)	11 (21)	0.508
Diastolic blood pressure (mm Hg)	64 ± 13	67 ± 18	0.390
Heart rate (bpm)	74 ± 15	77 ± 25	0.422
Hypertension	22 (46)	28 (47)	0.867
Diabetes mellitus	5 (10)	10 (16)	0.327
Hypercholesterolemia	26 (57)	23 (40)	0.087
Current smoking	24 (50)	29 (51)	0.929
Prior myocardial infarction	37 (73)	53 (87)	0.057
Prior percutaneous coronary intervention	51 (100)	62 (100)	
Prior coronary artery bypass grafing	4 (7.8)	4 (6.5)	0.774
Indication for initial stent placement			0.920
Stable angina pectoris	1 (2.0)	2 (3.2)	
Unstable angina pectoris	14 (28)	16 (26)	
NSTEMI	6 (12)	9 (15)	
STEMI	27 (54)	34 (55)	
Other	2 (4.0)	1 (1.6)	
Initial stent placement			0.461
Bare-metal stent	38 (75)	49 (80)	
Drug-eluting stent	13 (25)	12 (20)	
Total stent length (mm)	27 ± 15	27 ± 18	0.578
Minimal stent diameter (mm)	3.2 ± 0.5	3.2 ± 0.4	0.307
Multiple stent placement	17 (33)	18 (29)	0.623
ARC classification			0.009
Early stent thrombosis	25 (49)	34 (55)	
Late stent thrombosis	8 (16)	20 (32)	
Very late stent thrombosis	18 (35)	8 (13)	
Presentation			0.062
NSTEMI	3 (6.1)	11 (18)	
STEMI	46 (94)	50 (82)	
Medication use on admission			
Aspirin	31 (69)	38 (69)	0.983
Clopidogrel	22 (48)	34 (61)	0.193
Anticoagulant	8 (18)	13 (24)	0.474
Ischemic time (min), median (IQR)	149 (108 - 220)	173 (128 - 272)	0.109

Values are mean ± standard deviation, n (%), or median (interquartile range)

ARC, Academic Research Consortium; IQR, interquartile range; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

procedures for ST were performed between May 2002 and July 2010.

Baseline and procedural characteristics

Baseline characteristics at the time of the ST event are shown in Table 1. Both groups were well balanced with regard to baseline characteristics with no significant differences in age, sex, cardiovascular risk profile, and indication for initial bare-metal or drug-eluting stent placement. However, timing of ST by ARC classification differed between the two groups (P=0.009), with similar rates of early ST (49% vs. 55%), but lower rates of late ST (16% vs. 32%) and higher rates of very late ST (35% vs. 13%) in the thrombus aspiration group compared with the conventional PCI group. Furthermore, 94% of patients in the thrombus aspiration group presented as STEMI compared with 82% in the conventional PCI group (P=0.062).

Patients treated with thrombus aspiration exhibited similar rates of multivessel coronary disease (47% vs. 53%; P=0.510) and preprocedural TIMI 0 flow (84% vs. 89%; P=0.493) compared with patients treated with conventional PCI (Table 2). However, the left anterior descending artery was less frequently the target coronary artery in the thrombus aspiration group compared with the conventional PCI group (39% vs. 61%). Balloon dilatation after thrombus aspiration was performed in 80% of patients in the thrombus aspiration group, while balloon dilatation was performed in all patients in the conventional PCI group (P<0.001). Additional stent placement was performed in equal percentages of patients in the thrombus aspiration and conventional PCI groups (61% vs. 65%; P=0.683).

Procedural result

Procedural results are listed in Table 3. Post PCI, TIMI flow was significantly better in the thrombus

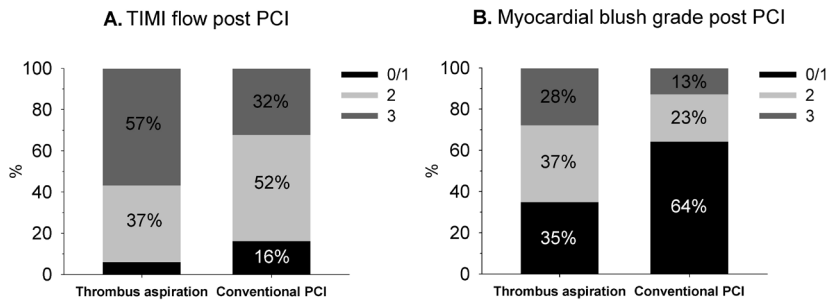

Figure 1. Myocardial reperfusion measures as assessed by (A) TIMI flow and (B) myocardial blush grade. TIMI flow and myocardial blush grade were significantly higher in patients treated with thrombus aspiration as compared with conventional PCI (P=0.006 and P=0.011, respectively).

Table 2. Procedural characteristics

Variable	Thrombus aspiration *(n=51)*	Conventional PCI *(n=62)*	P
Target coronary artery			0.069
Right	19 (37)	17 (27)	
Left anterior descending	20 (39)	38 (61)	
Circumflex	10 (20)	6 (9.7)	
Left main	0 (0)	1 (1.6)	
Graft	2 (3.9)	0 (0)	
Lesion calcium	19 (38)	23 (38)	0.975
Bifurcation lesion	17 (34)	29 (48)	0.150
Multivessel coronary disease	24 (47)	32 (53)	0.510
Preprocedural TIMI thrombus grade			0.787
≤3	1 (2.0)	1 (1.6)	
4	7 (14)	6 (9.7)	
5	43 (84)	55 (89)	
Preprocedural TIMI 0 flow	43 (84)	55 (89)	0.493
Balloon dilatation	41 (80)	62 (100)	<0.001
Additional stent placement	31 (61)	40 (65)	0.683
Bare-metal stent	20 (39)	30 (48)	0.329
Drug-eluting stent	11 (22)	10 (16)	0.459
Total stent length (mm)	26 ± 17	22 ± 12	0.488
Minimal stent diameter (mm)	3.3 ± 0.5	3.3 ± 0.4	0.871
Multiple stent placement	8 (16)	15 (24)	0.264
Intra-aortic balloon pump use	6 (12)	14 (23)	0.134
Glycoprotein IIb/IIIa inhibitor use	38 (75)	49 (79)	0.570

Values are mean ± standard deviation or n (%)
TIMI, thrombolysis in myocardial infarction

aspiration group (P=0.006; Figure 1). TIMI 3 flow was established in 57% of patients in the thrombus aspiration group compared with 32% of patients in the conventional PCI group. Better myocardial reperfusion in the thrombus aspiration group was also apparent from differences in the postprocedural myocardial blush grade (P=0.011; Figure 1). Myocardial blush grade 2 or 3 was established in 65% of patients in the thrombus aspiration group compared with 36% of patients in the conventional PCI group. Occurrence of distal embolization was lower in the thrombus aspiration group compared with the conventional PCI group (14% vs. 37%; P=0.017). In multivariable analysis, the use of thrombus aspiration was an independent predictor of postprocedural TIMI 3 flow (odds ratio 3.16; 95% confidence interval 1.22 – 8.17; P=0.018) and was selected in 86% of the bootstrap models (Table 4). The use of thrombus aspiration also predicted postprocedural myocardial blush grade 2 or 3 after multivariable adjustment (odds ratio 3.20; 95%

Table 3. Procedural result

Variable	Thrombus aspiration *(n=51)*	Conventional PCI *(n=62)*	P
TIMI flow			0.006
0/1	3 (5.9)	10 (16)	
2	19 (37)	32 (52)	
3	29 (57)	20 (32)	
MBG			0.011
0/1	15 (35)	25 (64)	
2	16 (37)	9 (23)	
3	12 (28)	5 (13)	
Distal embolization	6 (14)	15 (37)	0.017
TIMI thrombus grade ≥1	17 (34)	29 (48)	0.150
Side branch occlusion	3 (6.4)	14 (23)	0.021

Values are n (%)

MBG, myocardial blush grade; TIMI, thrombolysis in myocardial infarction

confidence interval 1.20 – 8.55; P=0.020) and was selected in 73% of the bootstrap models. There was no evidence for lack of fit in the final models as assessed by the Hosmer Lemeshow test (P=0.241 and P=0.911, respectively).

Data on successful retrieval of thrombotic material during thrombus aspiration was available in 37 patients in the thrombus aspiration group. In this group, thrombus aspiration was successful in 29 patients (78%). In 6 patients, histopathological analysis of aspirates was performed. Of these, we found thrombus with an erythrocyte component in 5 patients. Atheromatous plaque components were found in none of the aspirates. Aspirated thrombus was remarkably large; in 4 patients thrombus >2 mm was aspirated, in 1 patient thrombus sized 1-2 mm was aspirated, and in 1 patient only residue thrombotic material was retrieved.

Clinical outcome

At 30 days, mortality was 9.8% in the thrombus aspiration group and 16% in the conventional PCI group (P=0.351). Other clinical endpoints in the thrombus aspiration group and conventional PCI group at 30 days were myocardial infarction 4.2% vs. 7.3% (P=0.551), re-ST 4.2% vs. 5.3% (P=0.819), TVR 11% vs. 15% (P=0.589), and MACE 20% vs. 31% (P=0.221), respectively. At 1 year, the cumulative mortality was 12% in the thrombus aspiration group and 21% in the conventional PCI group (P=0.220; Figure 2). Other clinical endpoints in the thrombus aspiration group and conventional PCI group at 1 year were myocardial infarction 15% vs. 15% (P=0.856), re-ST 9.8% vs. 11% (P=0.758), TVR 22% vs. 23% (P=0.791), and MACE 34% vs. 41% (P=0.391), respectively.

When stratified by timing of ST by ARC classification, 30-day mortality was 20% for patients with early ST, 7.1%

Table 4. Predictors of procedural result by logistic regression with bootstrap selection

Dependent variable	Covariable	Odds ratio (95% CI)	P
Postprocedural TIMI 3 flow	Lesion calcium	5.78 (2.08 - 16.08)	0.001
	Bifurcation lesion	0.21 (0.08 - 0.58)	0.003
	Use of thrombus aspiration	3.16 (1.22 - 8.17)	0.018
	Bare-metal stent placement	0.25 (0.09 - 0.66)	0.006
	Multiple stent placement	7.01 (2.06 - 23.92)	0.002
Postprocedural MBG 2 or 3	Anticoagulant use on admission	0.26 (0.07 - 0.99)	0.048
	Use of thrombus aspiration	3.20 (1.20 - 8.55)	0.020

All procedural data refers to the stent thrombosis related procedure

CI, confidence interval; MBG, myocardial blush grade; TIMI, thrombolysis in myocardial infarction

for patients with late ST, and 3.8% for patients with very late ST (late ST vs. very late ST: P=0.590). At 1 year, these rates were early ST 27%, late ST 7.1%, and very late ST 3.8% (late ST vs. very late ST: P=0.590).

DISCUSSION

In the present observational study, we found that patients with ST treated with manual thrombus aspiration as compared with conventional PCI exhibited better postprocedural epicardial and microvascular coronary reperfusion as assessed by TIMI flow and myocardial blush grade, respectively. We observed a high rate of successful retrieval of thrombotic material in patients treated with thrombus aspiration. Better myocardial reperfusion translated into numerically lower 1-year mortality in patients treated with thrombus aspiration, although this did not reach statistical significance. Thereby, our study adds to the growing body of evidence in favor of the use of thrombus aspiration for ST,[10-12] and, to our knowledge, represents the largest series to date.

It is becoming increasingly clear that ST is a distinct clinical entity often lacking satisfactory myocardial reperfusion and clinical outcome.[13-15] Patients with ST often present with a large thrombus burden and distal embolization,[13] both of which have been related to adverse outcome.[7,16] The beneficial effects of thrombus aspiration for ST we observed in our study may be explained by the removal of local thrombus, thereby limiting macrovascular and microvascular obstruction and preventing distal embolization. In addition to removal of local thrombus, thrombus aspiration may improve myocardial reperfusion through several other mechanisms. First, fewer patients treated with thrombus aspiration required balloon dilatation. Prior

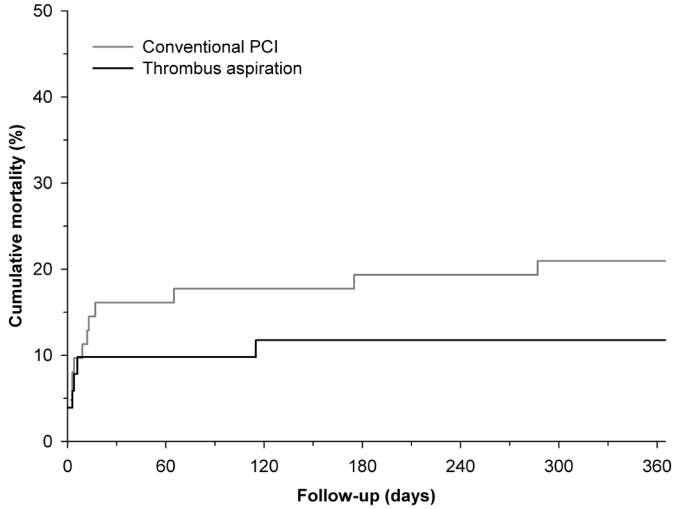

Figure 2. One year cumulative all-cause mortality by treatment group. One year mortality was 12% in the thrombus aspiration group and 21% in the conventional PCI group (P=0.220).

studies have suggested that balloon dilatation may mobilize thrombus and induce distal embolization.[17] Second, once present, distal emboli may be removed by the use of thrombus aspiration in some patients, as has been shown previously in patients with acute myocardial infarction.[18] Indeed, we observed a lower rate of postprocedural distal embolization in the thrombus aspiration group. Third, patients treated with thrombus aspiration exhibited lower rates of side branch occlusions. Although the clinical implications of this procedural complication are not well known,[19] some studies have suggested that side branch occlusions and distal embolization may be the main causes of periprocedural troponin release, a prognosticator of adverse clinical outcome.[20]

In 6 patients treated with thrombus aspiration, histopathological data was available. In these patients, we mainly retrieved large sized thrombus containing platelets and erythrocytes, but no plaque components. This thrombus composition is markedly different from a de novo STEMI population, where retrieved thrombus is generally smaller and plaque components are present in about 17% of patients.[1] Although the numbers in our study were small, this finding is in line with the growing awareness that ST also differs from de novo coronary thrombosis on a pathophysiological level. Prior studies have suggested that thrombus in patients with ST is relatively platelet rich and has a lower fibrin composition and a denser fibrin structure, compared with thrombus in patients with de novo coronary

thrombosis.[21-23] These properties may, in part, explain the limited success of reperfusion currently seen with fibrinolysis and PCI.

Some remarkable predictors of myocardial reperfusion in our ST population were found in our multivariable analyses. For instance, bare-metal stent placement was a predictor of lower postprocedural TIMI flow and anticoagulant use on admission predicted lower postprocedural myocardial blush grade. Most likely, these variables identify a subset of patients with more comorbid conditions (e.g. bare-metal stent placement for a patient with concomitant malignancy) and poorer procedural result, rather than directly explaining procedural result. Other factors, such as thrombus aspiration[10-12] and bifurcation lesion[24] are more likely to exert a direct effect on procedural result, considering previous studies. Importantly, target coronary artery was not predictive of postprocedural TIMI 3 flow nor myocardial blush grade 2 or 3. At baseline, the thrombus aspiration group contained equal percentages of patients with early ST, but more patients with very late ST and fewer patients with late ST, compared with the conventional PCI group. According to some reports, the ARC classification 'late ST'[25] or 'very late ST'[14] may be a predictor of mortality in patients with ST. To address this issue, we also analyzed mortality by timing of ST according to the ARC classification. We found that mortality was equal in patients with late and very late ST, but worse in patients with early ST. These results suggest no important confounding of clinical outcome by ARC classification in our study groups.

Limitations

It is important to consider several limitations of our study. First, the observational design of this study makes it susceptible to selection bias with regard to treatment allocation. However, baseline characteristics in the two groups were generally well balanced and not suggestive of selection bias. Moreover, we tried to adjust for potential confounders by multivariable adjustment. Still, we can not fully exclude the possibility of confounding by baseline factors that we did not study. Second, the sample size of our study was small, as is often the case in the relatively limited population of patients with ST. Therefore, it is likely that this study was not sufficiently powered to detect differences in clinical outcome. However, the widely accepted surrogate markers for outcome, TIMI flow and myocardial blush grade, did show a clear advantage for thrombus aspiration over conventional PCI. In addition, it is unlikely that improvements in the treatment of patients with ST will come from adequately powered randomized clinical trials due to the low incidence of ST.

CONCLUSIONS

The use of manual thrombus aspiration in patients with ST was associated with greater epicardial and microvascular myocardial reperfusion. Fewer procedural complications such as distal embolization and side branch occlusions occurred in patients treated with thrombus aspiration. In addition, mortality was lower in these patients, although this did not reach statistical significance.

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